

Testimony
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Prostate Cancer Research at the National Institutes of Health

Statement of
William Dahut, M.D.
Clinical Director, NCI
Chief, GU/GYN Clinical Research Section
Medical Oncology Branch
National Cancer Institute
National Institutes of Health
U.S. Department of Health and Human Services

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Thank you for the opportunity to speak to you today. I am Dr. Bill Dahut, Clinical Director of the National Cancer Institute (NCI) and Chief of the GU/GYN Clinical Research Section within the Medical Oncology Branch at the NCI within the National Institutes of Health (NIH), an agency of the Department of Health and Human Services (HHS). The National Cancer Institute is dedicated to the understanding, diagnosis, treatment, and prevention of cancer. Our research portfolio in prostate cancer seeks to increase our understanding of the disease and to improve outcomes for men with prostate cancer, and includes research on screening and imaging, treatment, and health disparities. My particular research focuses on the development of novel therapeutic strategies for the treatment of prostate cancer.

Prostate cancer is the second highest cause of cancer deaths for men in the United States, second only to lung cancer. American men have a 1 in 6 chance of being diagnosed with prostate cancer within their lifetime, and the incidence increases markedly as men age. The good news is that overall death rates from prostate cancer are on the decline. This improvement is thought likely to be from a combination of earlier detection and improvements in treatment. The bad news is that we are still struggling to differentiate lethal prostate cancer from non-lethal prostate cancer, which is the most significant factor in deciding how to treat the disease. Another unfortunate reality is that the burden of prostate cancer is disproportionately borne by African American men, who have a 60% higher incidence of prostate cancer as compared to white men, and are twice as likely to die from their disease.

It is important to understand that prostate cancer is not like most other cancers. Most prostate cancers grow very slowly and never cause problems. But a few grow quickly and spread through the body. The single biggest challenge for researchers is to identify lethal from non-lethal disease and to determine the best way to approach treatment. There are three standard treatments for early prostate cancer: surgery, radiation, and “active surveillance.” It is difficult to determine which treatment option is most appropriate for a particular patient. Research has shown that, in general, younger men with larger tumors live longer if they opt for surgery as opposed to observation. However, it is likely that there are men with indolent (i.e., not aggressive) disease, in whom surgery not only would be unnecessary, but also could potentially produce debilitating side effects. To determine the best choice for a man with early prostate cancer, we need to better understand the characteristics of his tumor. For instance, if a physician knew that a particular tumor was life-threatening, then an aggressive treatment approach could be selected, but if the tumor was indolent, then possibly no treatment would be needed. NCI is moving vigorously toward this goal by researching genetic analyses, molecular characterization, and imaging techniques that will help to differentiate the aggressive prostate cancers from the less bothersome ones.

Prostate cancer remains a high research priority for the NIH. In Fiscal Year (FY) 2009, NIH devoted approximately \$310 million towards prostate cancer research, and an additional \$47 million was devoted to prostate cancer research from funds provided under the American Recovery and Reinvestment Act of 2009 (ARRA). For FY 2010, \$319 million in funding is expected, with an additional \$26 million in funding under ARRA. And the President’s budget request for FY 2011 includes an estimated \$329 million. With these funds, NIH is supporting researchers nationwide studying ways to better detect prostate cancer and to determine which prostate cancers will be aggressive.

For example, a recent NCI-funded study found that screening with the prostate-specific antigen (PSA) blood test, while capable of detecting the presence of prostate cancer, was not effective in reducing mortality. There are some concerns that results from this trial were confounded when men who did not receive PSA screening as part of the trial checked their PSA values independently, but despite this concern, it appears that the

impact of PSA on overall mortality is likely to be small. Notably, PSA alone does not differentiate which men have those aggressive forms of prostate cancer that are likely to lead to pain and suffering from cancer. Another challenge for screening is the poor specificity, or high rate of false negatives, of the current screening approaches (PSA testing and digital rectal exam). This means that important treatment decisions require confirmatory evidence from prostate tissue biopsies. However, traditional biopsy procedures do not always successfully identify and obtain sample malignant tissue, which may lead to significant under-diagnosis of potentially lethal cancers. Researchers are trying to address this problem by developing novel image-guided prostate biopsy approaches. NIH's National Institute of Biomedical Imaging and Bioengineering (NIBIB) is currently funding a study at Johns Hopkins University that is developing a novel MRI-compatible robot that will substantially decrease the "false negative" rate and increase the accuracy for standard prostate cancer biopsy procedures.

NCI is actively searching for other biomarkers -- substances that may be found in tumor tissue or released from a tumor into the blood or other body fluids such as urine -- that will distinguish between cancerous and benign conditions, and between slow-growing cancers and fast-growing, potentially lethal cancers. The identification of such biomarkers is a high priority in order to provide safe and effective large population screening.

Nanotechnology is providing new opportunities for prostate cancer treatment. NCI's Alliance for Nanotechnology, a program that brings together science and technology and applies them to cancer research, has yielded exciting findings for prostate cancer. In late 2009, a team at Northwestern University used gold nanoparticle probes to recognize and detect PSA at very low levels - 300 times more sensitive than commercially available PSA tests. This new assay could be used to monitor PSA in post-surgery patients and pinpoint optimal timing to target further treatment. Other NCI research has shown how to target nanoparticles to detect and destroy prostate tumors, ensuring that only the cancer cells get the chemotherapy drug. This represents a great opportunity to maximize anti-tumor impact while minimizing toxicities associated with chemotherapy.

Imaging studies can also be important tools in helping to determine which prostate cancers are aggressive and which are slow growing, as well as in developing minimally invasive treatments. Specialized imaging can help monitor men who elect active surveillance, and improved imaging techniques may allow more accurate characterization of disease and more sophisticated methods of monitoring response to therapy. Better imaging capabilities would allow us to plan the most appropriate treatments for a specific patient, including focal, prostate-sparing therapies, and to gauge success or failure of a therapy more quickly. There are many different imaging tools available, but currently there is no clear consensus within the field about the best ways to integrate imaging into clinical management. NCI is working toward bringing imaging experts together to standardize an approach to apply imaging measurements to clinical outcomes.

NCI research efforts in prostate cancer imaging are geared towards developing an accurate method for identifying prostate cancer and directing treatments to the tumor under image guidance, detecting recurrent disease, and monitoring tumor that has spread outside the prostate. Part of our research effort focuses on creating image-guided procedures that fuse magnetic resonance imaging (MRI) data with Ultrasound in order to guide interventions based on the imaging findings. Additional goals are to better understand the biology of low-grade prostate cancer and how to differentiate aggressive tumors using imaging. We are also investigating imaging agents that could monitor the effects of treatments for more advanced disease. Ultimately, we seek to develop targeted therapies for prostate cancer that will be more effective for the specific individual's prostate tumor with fewer side effects. Progress in prostate cancer imaging is already beginning to translate into better treatment selection and accurate imaging-guided therapies, including focal ablation and customized surgery and radiation. It is hoped that these advances in imaging will improve detection, treatment, and clinical outcomes for prostate cancer.

NCI broadly supports the development of new technologies that will help us not only diagnose prostate cancer earlier, but also determine more specific information about the characteristics of individual tumors to enable more effective treatments. In addition to cancer imaging methods and nanotechnology, NCI is also studying genetic factors at play in prostate cancer as well as proteomics, which is the study of the structure and function of proteins, to develop methods to identify cancers at an earlier stage.

Genomics and proteomics are playing an important role in NCI's research efforts for all cancers. Data from the pilot phase of The Cancer Genome Atlas (TCGA), a genomic sequencing and analysis program being conducted jointly with NIH's National Human Genome Research Institute, has generated remarkable insights into glioblastoma and ovarian cancer. The data suggest that initiating a whole genome sequencing project for prostate cancer would likely provide us with the genomic information necessary to discriminate between low risk and high risk prostate cancer. NIH has just expanded TCGA to include prostate cancer in the 20 new cancers to be studied in the next phase of TCGA. This should yield a wealth of important data on the genomics of prostate cancer.

It is clear that prostate cancer is a complex and diverse entity, and combining the knowledge of genomic, proteomic, imaging and clinical behavior into the evolving field of "systems biology" will lead to a better understanding of the origins of prostate cancer and its cure. The NCI Clinical Center team is studying new therapeutic approaches to prostate cancer through various clinical trials. An NCI-developed prostate cancer vaccine has shown significant benefit in a Phase II study at the NIH and will be moving into larger clinical trials soon. NCI has also participated in the research and development of a prostate cancer vaccine called Provenge that is currently undergoing FDA review for approval.

NCI funds investigators across the country to develop and test new therapeutic research strategies for prostate cancer. As part of an NCI-wide program aimed at identifying new opportunities in prostate cancer research, the NCI has expanded the prostate cancer Specialized Program of Research Excellence (SPORE) program from 2 funded prostate SPOREs in 1992 to 10 SPOREs in 2009 with a total budget of over \$19 million. This program has developed new scientific approaches in early detection, diagnosis, treatment, and prognosis of human prostate cancer. The SPOREs in prostate cancer have evolved into a collaborative network, with experts across the country conducting their inter-SPORE scientific studies for the clinical evaluation of biomarkers, early phase clinical trials of anti-prostate cancer agents, and the development of inter-institutional systems to accelerate prostate cancer research.

In addition to the SPOREs, NCI's extramural research portfolio includes the 65 NCI-designated Cancer Centers, centers that are characterized by scientific excellence and the capability to integrate a diversity of research approaches to focus on the problem of cancer. They play a vital role in advancing towards our goal of reducing morbidity and mortality from all cancers.

The NCI has also heavily invested in its Clinical Trials Cooperative Groups and Community Clinical Oncology Program (CCOP). Both of these programs conduct clinical trials designed to study new cancer treatments, explore methods of cancer prevention and early detection, and study quality-of-life issues and rehabilitation during and after treatment. NCI's Cooperative Groups provide access to prostate cancer clinical trials in every state through an extensive network of cooperative groups and community based study sites. The CCOP program brings clinical trial expertise to the community level and ensures broad access to clinical trials across populations and geographic areas. The program supports groups of community hospitals and physicians funded by a peer-reviewed cooperative agreement to participate in NCI-sponsored cancer treatment, prevention, and control clinical trials. A subgroup of the CCOPs, the Minority-Based-CCOPs (MB-CCOPs), were established to connect academic centers with community physicians in underserved and minority communities. Forty percent of new cancer patients in Minority-Based CCOPs are from minority populations. This is particularly important in studying diseases such as prostate cancer that has a higher incidence and mortality in African-American men as compared to other racial groups.

Through these innovative programs, NCI is providing access to state-of-the-art approaches to early detection and treatment of prostate and other cancers to people in the communities in which they live.

In light of the fact that prostate cancer occurs and causes death more frequently in African-American men than other racial groups, health disparities is a particularly important area of prostate research. We have learned that complex and interrelated factors contribute to the observed disparities in cancer incidence and death among racial, ethnic, and underserved groups. The most obvious factors are associated with a lack of

health care coverage and low socioeconomic status (SES). SES factors, such as a person's income, education level, occupation, access to health insurance, and living conditions, are associated with the risk of developing and surviving cancer. Behavioral risk factors, such as tobacco use, obesity, and excessive alcohol intake, are influenced by SES, and people with low SES are also less likely to follow cancer screening recommendations. Research also shows that individuals from medically underserved populations are more likely to be diagnosed with late-stage diseases that might have been treated more effectively or cured if diagnosed earlier.

The higher incidence of prostate cancer in African American/Black men compared with men from other racial/ethnic groups prompted the hypothesis that genetic factors might account, in part, for the observed differences. Recent findings from NCI's Cancer Genetic Markers of Susceptibility (CGEMS) program (<http://cgems.cancer.gov>) and other investigations support this hypothesis. Researchers have identified changes—called variants—in human DNA that are associated with the risk of developing prostate cancer. Different combinations of these variants have been found in men from different racial/ethnic backgrounds, and each combination is associated with higher or lower risk for prostate cancer. Nearly all of the variants associated with an increased risk of developing prostate cancer were found most often in African American/Black men, and certain combinations of these variants were associated with a five-fold increased risk of prostate cancer in men of this racial/ethnic group.

NCI's Center to Reduce Cancer Health Disparities (CRCHD), headed by Dr. Sanya Springfield, is central to the NCI's efforts to reduce the unequal burden of cancer in our society and to train the next generation of competitive researchers in cancer and cancer health disparities research. CRCHD initiates, integrates, and engages in collaborative research studies with other NCI divisions and with other NIH Institutes and Centers to promote research and training in cancer health disparities research and to identify new and innovative scientific opportunities to improve cancer outcomes in communities experiencing an excess burden of cancer.

An important component of CRCHD's efforts to address this challenge is through the Continuing Umbrella of Research Experiences (CURE), which is a comprehensive training and career development program that seeks to increase the number of competitive cancer researchers who are currently conducting research in cancer health disparities. Since the inception of CURE in 1997, approximately 16% of the pre-doctoral trainees and 10% of the junior investigators that were supported have conducted research in the area of prostate cancer.

CRCHD supports a broad portfolio of prostate cancer research that includes a study of a preventive vaccine for prostate cancer that stimulates the immune system to attack tumor cells. This is an important research area because an effective prostate cancer vaccine would protect against disease and decrease doctor visits and the need for extensive follow up, factors that are important for the African American community that has less access to

care and lower utilization of health care resources overall. CRCHD is also examining ways to increase education and awareness about prostate cancer in the African American and Hispanic communities through new types of media and community programs. For example, funded programs include a Spanish language radio talk show about prostate cancer, training for African American barbers to educate clients about prostate cancer, and the use of church settings to provide screening and prevention information to specific communities.

NIH continues to partner with academic researchers, community-based physicians, and the advocacy community to advance prostate cancer research. In April of this year, NCI will hold the first collaborative meeting with the Prostate Cancer Foundation to gather the nation's leading investigators in the treatment sciences of metastatic prostate cancer. This group will explore and define cutting-edge approaches to the scientific treatment of advanced prostate cancer patients. We expect to reconvene this group on a yearly basis to exchange data and explore new frontiers in prostate cancer research.

We are optimistic that through the application of new technologies and innovative approaches to detecting, assessing, and treating prostate cancer, we will be able to better understand of this disease and thus, more effectively identify and treat the aggressive forms of this disease, thereby reducing death and suffering from prostate cancer.

Thank you for the opportunity to testify.

Dr. William Dahut received his M.D. from Georgetown University in Washington, D.C. He completed clinical training in internal medicine at the National Naval Medical Center in Bethesda, Md., followed by training in hematology and medical oncology at the Bethesda Naval Hospital and the Medicine Branch of NCI. Dr. Dahut worked as an attending physician in the NCI-Navy Medical Oncology Branch until 1995. He then joined the faculty of the Lombardi Cancer Center at Georgetown University before returning to the former NCI Medicine Branch in 1998 as head of the prostate cancer clinic. Dr. Dahut is the clinical director of NCI and chief of the GU/GYN Clinical Research Section in the Medical Oncology Branch. Dr. Dahut's primary research interest has been in the development of novel therapeutic strategies for the treatment of adenocarcinoma of the prostate.